Prostate Cancer and Supplementation With α-Tocopherol and β-Carotene: Incidence and Mortality in a Controlled Trial

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Background: **Epidemiologic studies have suggested that vitamin E and β-carotene may each influence the development of prostate cancer. In the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, a controlled trial, we studied the effect of α-tocopherol (a form of vitamin E) and β-carotene supplementation, separately or together, on prostate cancer in male smokers.** ***Methods:*** **A total of 29 133 male smokers aged 50–69 years from southwestern Finland were randomly assigned to receive α-tocopherol (50 mg), β-carotene (20 mg), both agents, or placebo daily for 5–8 years (median, 6.1 years). The supplementation effects were estimated by a proportional hazards model, and two-sided *P* values were calculated.** ***Results:*** **We found 246 new cases of and 62 deaths from prostate cancer during the follow-up period. A 32% decrease (95% confidence interval [CI] = −47% to −12%) in the incidence of prostate cancer was observed among the subjects receiving α-tocopherol (n = 14 564) compared with those not receiving it (n = 14 569). The reduction was evident in clinical prostate cancer but not in latent cancer. Mortality from prostate cancer was 41% lower (95% CI = −65% to −1%) among men receiving α-tocopherol. Among subjects receiving β-carotene (n = 14 560), prostate cancer incidence was 23% higher (95% CI = −4%–59%) and mortality was 15% higher (95% CI = −30%–89%) compared with those not receiving it (n = 14 573). Neither agent had any effect on the time interval between diagnosis and death.** ***Conclusions:*** **Long-term supplementation with α-tocopherol substantially reduced prostate cancer incidence and mortality in male smokers. Other controlled trials are required to confirm the findings. [J Natl Cancer Inst 1998;90:440–6]**

Clinical prostate cancer incidence and mortality vary greatly between populations, whereas the prevalence of latent cancer at autopsy is remarkably similar *(1–3)*. Wide geographic variation and increasing incidence after migration to high-risk areas suggest that environmental factors are important in the etiology of invasive prostate cancer. Risk indicators include dietary factors, obesity, sexual behavior, occupation, cadmium exposure, and infectious agents *(1,2,4–6)*.

The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC Study) was a randomized, double-blind, placebo-controlled primary-prevention trial to test the hypothesis that supplementation with α-tocopherol (a form of vitamin E) or β-carotene reduces cancer incidence *(7,8)*. This article describes the effects of these supplements on prostate cancer incidence and mortality.

Subjects and Methods

The ATBC Study was designed primarily to explore the prevention of lung cancer; therefore, all participants were smokers (five or more cigarettes per day). They were recruited from the total male population of 290 406, aged 50–69 years, residing in southwestern Finland from 1985 through 1988. Subjects with prior cancer, serious disease limiting the capacity to participate, or use of vitamin E, vitamin A, or β-carotene supplements were excluded. The rationale, methods, participant characteristics, compliance, and main results of the ATBC Study have been reported *(7–9)*.

At baseline, each subject's medical and smoking history was obtained, height and weight were recorded, and a sample of serum was collected. Dietary intakes of vitamin E and β-carotene were estimated from a diet history questionnaire *(10)*, while serum concentrations of α-tocopherol and β-carotene were determined by high-performance liquid chromatography *(11)*.

Participants (n = 29 133) were randomly assigned within each study area (n = 14) to one of the four intervention groups of α-tocopherol alone (n = 7286), β-carotene alone (n = 7282), α-tocopherol and β-carotene (n = 7278), or placebo (n = 7287). The dose of α-tocopherol was 50 mg and that of β-carotene was 20 mg as a single capsule daily. The study agents were synthetic *dl*-α-tocopheryl acetate (50% powder) and synthetic β-carotene (10% water-soluble beadlets) provided by Hoffmann-La Roche Ltd., Basel, Switzerland. A two-by-two factorial design allowed assessment of both agents independently. Thus, one half of the participants received α-tocopherol (n = 14 564) and one half did not (n = 14 569). Similarly, one half of the participants received β-carotene (n = 14 560) and one half did not (n = 14 573). Capsule supplementation continued for 5–8 years (median, 6.1 years) until April 1993, with a total of 169 247 person-years. None of the participants were lost to follow-up.

During their visits to the local study centers three times a year, the participants were asked about their medical contacts, including physician-diagnosed prostate cancer and prostatic hyperplasia. We identified those participants diagnosed with prostatic hyperplasia at a hospital through the national Hospital Discharge Register, which documents all hospitalizations in Finland. Participants were also asked about their self-perceived skin yellowing, which occasionally can disclose blindness of β-carotene supplementation. The remaining capsules were returned at each visit, and overall capsule compliance was estimated by dividing the total

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See "Notes" following "References."

number of nonreturned capsules by the number of days in the trial. Four of five participants received more than 95% of their capsules while in the trial. The dropout rate (including 3570 deaths) was 31%; contact with the surviving dropouts was maintained to the end of the study *(7–9)*.

A follow-up blood sample was taken after 3 years of supplementation. Prostate-specific antigen was determined by an immunofluorometric method *(12)* as an indirect measure of prostate enlargement from the baseline in paired baseline/3-year serum samples from 230 randomly selected men without diagnosed cancer.

The study protocol did not include the clinical examination of prostate size or consistency at any time. Prostate cancers (n = 246) were identified through the Finnish Cancer Registry and the Register of Causes of Death; both provide close to 100% of the case ascertainment nationwide *(13,14)*. Cases known to have been diagnosed up to April 30, 1993, are included in this article and case survival was followed through April 30, 1994. After the initial publication of the ATBC Study *(8)*, three additional prostate cancer cases were reported to the Cancer Registry and an additional seven cases were reclassified as nonmalignant in a subsequent pathology review. One of the deleted nonmalignant cases was in the α-tocopherol group and two were in each of the three other initial intervention groups.

Histopathologic and cytologic specimens from the patients with prostate cancer were obtained for central review from 31 pathology laboratories. Twenty-eight specimens were obtained following open prostatectomy, 74 following transurethral resection, 91 from needle biopsy, 68 from fine-needle aspiration, 10 from histologic biopsy of metastasis in various locations, and eight following autopsy. The slides were reviewed from 1992 through 1993 independently by two pathologists for cancer, histologic type, and histologic/cytologic grade. The diagnosis was adenocarcinoma in 98% of 195 cases with one or more histologic specimens. The histologic type could not be specified in two cases because the cells were highly anaplastic; one adenocarcinoma diagnosed by a hospital pathologist was not available for review.

The medical records of the patients with prostate cancer were reviewed centrally for diagnostic confirmation and staging by two clinical oncologists who worked independently but who used the results of the central histologic and cytologic review. A diagnosis of prostate cancer was based on histology in 79% of the patients, on cytology in 19%, and on clinical data only in 2% (four men). The proportions of these diagnostic methods did not differ among the trial supplementation groups ($P = .67$). A random sample of 84 prostate cancer cases was rereviewed by a urologist who confirmed all of the diagnoses.

Staging was based on the 1992 criteria for prostate cancer of the American Joint Committee on Cancer *(15)* and was undertaken during 1992 and 1993. Stage 0 and I tumors include clinically inapparent tumors, stage II tumors include clinically apparent tumors confined within the prostate, stage III tumors include those tumors extending through the prostate capsule, and stage IV tumors include those tumors fixed into or invading adjacent structures other than the seminal vesicles and all tumors with regional lymph node or distant metastasis. This scheme differs from the 1997 revision, which classifies clinically inapparent tumors as stage I and which recognizes prostatic intraepithelial neoplasia as a distinct disease entitity. In 123 cases, the oncologists considered the clinical examination inadequate to definitely exclude regional lymph node or distant metastases; of these, 43 cases involved clinically inapparent tumors (classification T1) and 80 cases involved clinically apparent tumors (T2 or T3) without any symptom or sign of tumor dissemination, and thus classified to be free of regional lymph node or distant metastasis.

Study staff involved in the end point review or laboratory determinations remained blind to intervention assignments until the assessments had been completed.

The main analyses estimating the effect of the supplementations on prostate cancer incidence and mortality were based on the intention-to-treat principle, i.e., follow-up and case count continued irrespective of dropout from trial participation. In these analyses, other cancers were ignored. Kaplan–Meier cumulative incidence curves and two-sided *P* values from the unweighted logrank statistic are presented for the initial intervention groups and separately for the α-tocopherol and β-carotene recipients and nonrecipients, after testing the interaction of the agents by the likelihood ratio test. The supplementation effects were estimated by the proportional hazards model *(16)* and are reported as a percentage change with 95% confidence interval (CI). The supplementation effects, possibly modified by baseline factors, were analyzed accordingly, with the factors divided by the median and the quartiles. The effect of alcohol was explored in more detail—because of its reported interaction with β-carotene in relation to lung cancer incidence *(9,17)*—by analyzing nondrinkers as one category and drinkers in tertiles. The results were also adjusted for age, number of cigarettes, years of smoking, and fat intake.

The interaction between prostatic hyperplasia and supplementation's effect on prostate cancer was tested by the proportional hazards model, using hyperplasia as the time-dependent covariate. The effect of self-perceived skin yellowing was evaluated by comparing the 1-year incidence of prostate cancer, after visits at which skin yellowing was reported, to the incidence following visits without such reported yellowing—as well as by adding skin yellowing to the models of supplementation effect as a time-dependent covariate. In analyses of participant-reported prostatic hyperplasia and skin yellowing, the intention-to-treat principle had to be abandoned because information was not available after study dropout. A hospital-based diagnosis of prostatic hyperplasia was available also for dropouts and was evaluated in relation to the supplementation effects according to the intention-to-treat principle.

The associations between the incidence of prostate cancer and baseline dietary intakes and serum concentrations of α-tocopherol and β-carotene in the absence of supplements were calculated in the placebo group by the proportional hazards model.

The study was approved by the review boards of the participating institutions. Participants gave informed written consent before randomization, and their interests were upheld by an outside Data and Safety Monitoring Committee twice a year throughout the trial.

Results

There were no differences in background factors between the intervention groups at baseline (Table 1). Capsule compliance and dropout rates were also similar across the intervention groups.

Three of four patients with prostate cancer visited a physician initially because of urinary symptoms and the remaining (one of four) visited a physician because of other symptoms, but complained additionally of urinary symptoms or had an abnormal prostate on clinical examination. These rates were similar in all supplementation groups. Only one case (in the placebo group) was initially detected through prostate-specific antigen screening.

Of the 54 patients with clinically inapparent (stage 0–I) cancer, 74% had contacted a physician primarily because of urinary symptoms and, in all but one, carcinoma was identified in the histologic sections obtained from transurethral resection; 19% had visited a physician primarily because of other symptoms, but either complained of urinary symptoms as well or were found to

Table 1. Baseline characteristics (median) of trial participants according to initial intervention group

	Intervention group*			
	AT	AT + BC	BC	Placebo
No. of subjects	7286	7278	7282	7287
Age, y	57.1	57.3	57.2	56.9
Cigarettes/day	20	20	20	20
Serum α-tocopherol, mg/L	11.5	11.6	11.5	11.5
Serum β-carotene, μg/L	168	172	170	171
Serum cholesterol, mmol/L	6.15	6.18	6.14	6.15
Body mass index, kg/m^2	26.0	26.0	25.9	26.0
Total energy intake, kcal/day	2736	2714	2720	2710
Total fat intake, g/day	118	117	118	116
Alcohol intake, g/day	11.3	10.8	11.0	10.8
Vitamin E intake, mg/day	10.2	10.3	10.3	10.2
β-Carotene intake, mg/day	1.64	1.67	1.65	1.67
History of prostatic hyperplasia, %	3.9	3.9	3.8	4.1

*AT = α-tocopherol supplementation and BC = β-carotene supplementation.

have an enlarged prostate during routine digital rectal examination; and 7% were found to have prostate cancer at autopsy, following death from other causes. Of the 192 patients with clinically overt (stage II–IV) cancer, 75% had visited a physician primarily because of urinary symptoms, and the remaining 25% saw a physician for other symptoms but were found to have a clinically abnormal prostate that led to a subsequent diagnosis of prostate cancer. Visiting a physician because of urinary symptoms was not related to the trial supplementation (clinically inapparent and overt cases combined; α-tocopherol—recipients 77% versus nonrecipients 72%, $P = .37$; β-carotene—recipients 75% versus nonrecipients 73%, $P = .87$).

The overall autopsy rates were similar in the supplementation groups: 52% in the α-tocopherol recipients and 55% in the nonrecipients and 54% in the β-carotene recipients and 53% in the nonrecipients. The same number of autopsies were done among patients with prostate cancer whether or not they received α-tocopherol (six versus six) or whether or not they received β-carotene (six versus six). Four cases were only diagnosed at autopsy (one in the α-tocopherol plus β-carotene group and three in the placebo group). Surgery and other treatments were equally distributed across the supplementation groups in those cancer patients who subsequently died. There were no surgery-related deaths. Approximately one half of the patients with prostate cancer continued on the trial supplementation regimen after diagnosis.

Of the 246 incident cases of prostate cancer, 43 were in the α-tocopherol-alone group, 56 were in the α-tocopherol plus β-carotene group, 80 were in the β-carotene-alone group, and 67 were in the placebo group. The cumulative incidences are shown in Fig. 1. Compared with the placebo group, the incidence in the α-tocopherol-alone group was 36% lower (95% CI = −56% to −6%), in the α-tocopherol plus β-carotene group was 16% lower (95% CI = −41% to 20%), and in the β-carotene-alone group was 20% higher (95% CI = −13% to 66%). There was no interaction between α-tocopherol and β-carotene supplementation effects (likelihood ratio test, $P = .75$).

Among men receiving α-tocopherol, the cumulative incidence of prostate cancer decreased progressively from the second year relative to those who did not receive α-tocopherol and resulted in a 32% difference (95% CI = −47% to −12%) (Fig. 2). In contrast, an increasing trend in the incidence of prostate cancer was observed in men receiving β-carotene compared with those not receiving it, but the 23% difference (95% CI = −4% to 59%) was not statistically significant (Fig. 3).

The incidence of clinical tumors (stage II–IV) decreased by 40% in subjects receiving α-tocopherol (95% CI = −55% to −20%) but increased 35% in subjects receiving β-carotene (95% CI = 1%–80%) (Table 2). Neither agent had a statistically significant effect on latent (stage 0–I) cancers. The results remained similar, even after excluding cases with insufficient information on regional lymph node status or distant metastasis.

There were 62 deaths from prostate cancer: 11 in the α-tocopherol-alone group, 12 in the α-tocopherol plus β-carotene group, 21 in the β-carotene-alone group, and 18 in the placebo group. The mortality from prostate cancer was 41% lower in men receiving α-tocopherol than in those not receiving it (95% CI = −65% to −1%) and 15% higher in men receiving β-carotene than in those not receiving it (95% CI = −30% to 89%). Supplementation did not influence survival time after diagnosis.

In 11 of the 14 study areas, the men receiving α-tocopherol exhibited lower prostate cancer incidence, and α-tocopherol decreased prostate cancer incidence similarly in subjects whose background factors were below or above the median values (Table 3). β-Carotene supplementation increased the risk of prostate cancer among men whose dietary intake of β-carotene (1.66 mg/day) or fat (117 g/day) was below the median, whereas no increased risk was observed at higher intake levels; these effects were mutually independent. The supplementation effects were also studied in quartiles of dietary intake and serum level of α-tocopherol and β-carotene at baseline. The results were in line with the analyses based on medians. β-Carotene appeared to decrease the risk of prostate cancer by 32% among nondrinkers, whereas among drinkers, the risk seemed to increase 25%, 42%, and 40% by tertiles (limits, 7.3 and 22.9 g/day); the differences of β-carotene effect between the four alcohol-drinking groups were not significant (P for trend = .17).

Among recipients of α-tocopherol, the rate of prostatic hyperplasia diagnosed in the hospital was 4% (95% CI = −16% to 8%) less—and hyperplasia caused 12% fewer visits to a physician (95% CI = −22% to −1%)—than for nonrecipients. Men who received β-carotene supplementation had a 6% (95% CI = −18% to 6%) lower rate of hyperplasia diagnosed in the hospital and made 5% fewer prostate-related visits to a physician (95% CI = −15%–7%). Irrespective of whether they remained in the trial, 917 men were found during the follow-up to have prostatic hy-

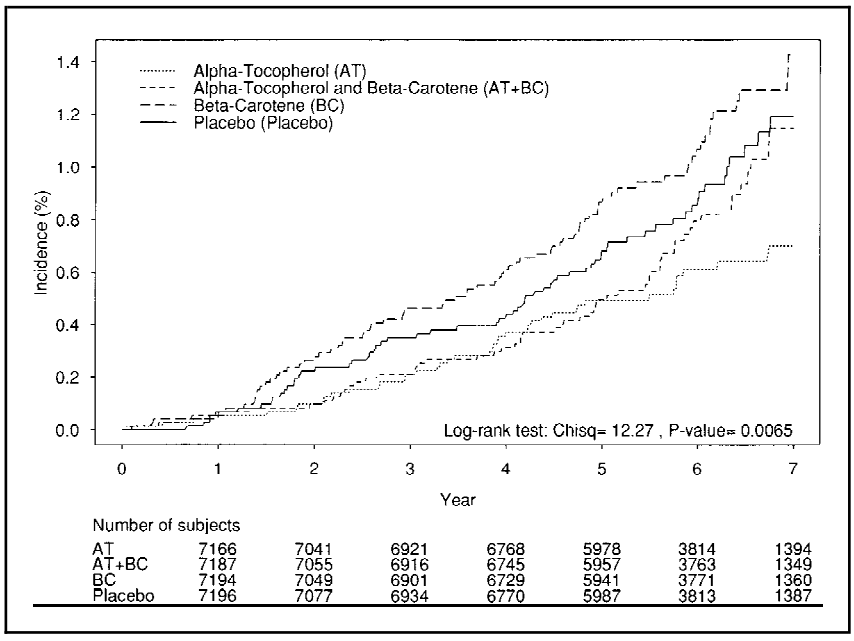

Fig. 1. Kaplan–Meier curves of the cumulative incidence (%) of prostate cancer, by initial intervention group.

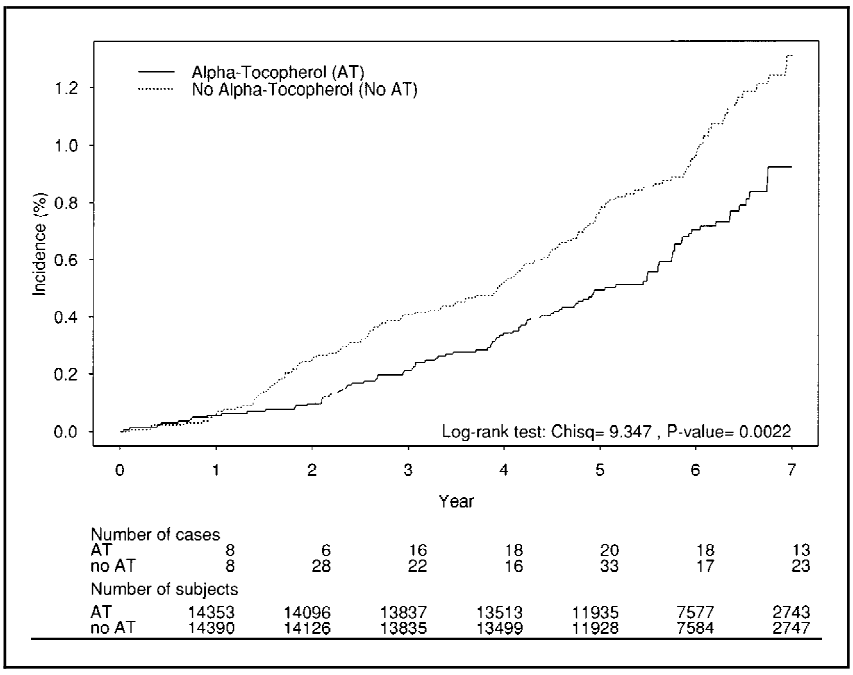

Fig. 2. Kaplan–Meier curves of the cumulative incidence (%) and annual number of prostate cancer cases among participants who did or did not receive α-tocopherol.

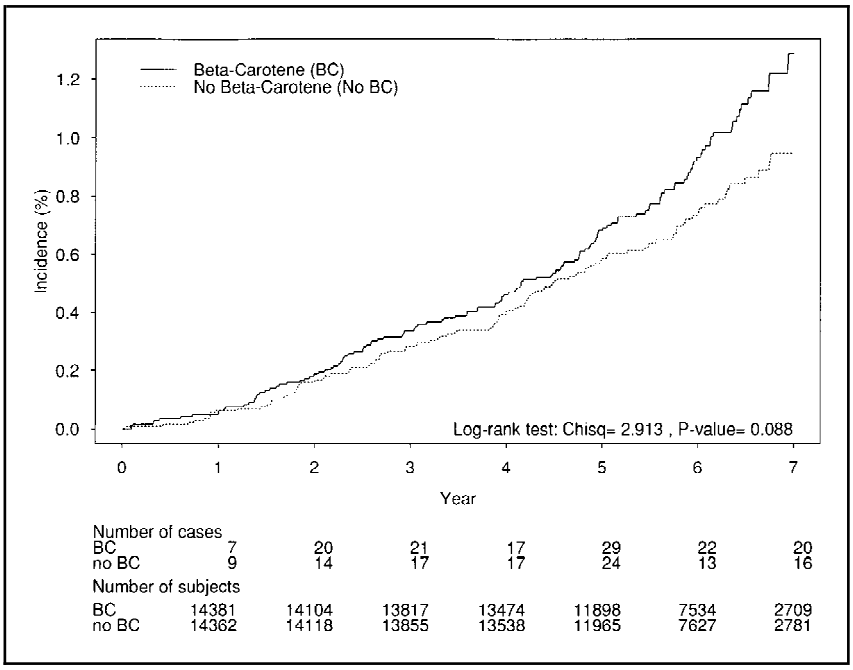

Fig. 3. Kaplan–Meier curves of the cumulative incidence (%) and annual number of prostate cancer cases among participants who did or did not receive β-carotene.

perplasia as their hospital discharge diagnosis. Hyperplasia and cancer diagnoses were present together more often than expected based on age-specific rates, occurring together in 63 men as opposed to an expected number of eight (Table 4). The majority of these men were diagnosed with latent (stage 0–I) prostate cancers; in contrast, cancers were latent in only one tenth of those men diagnosed with prostate cancer and who did not exhibit prostatic hyperplasia. The observation of supplementation effects was based primarily on those patients with prostate cancer who lacked any indication of prostatic hyperplasia. Joint diagnoses of hyperplasia and cancer often occurred during the same hospital stay in response to the same symptoms, making the order of diagnoses hard to determine. While α-tocopherol may have retarded growth of the enlarged prostate or relieved hyperplasia-related symptoms, a diagnosis of prostatic hyperplasia at visits to a physician during the study did not alter the vitamin's observed effect on prostate cancer incidence (change in incidence when hyperplasia reported, −38%; when not reported, −27%; $P = .57$). In a model with hyperplasia as the time-dependent covariate, the finding remained similar. Serum prostate-specific antigen concentrations rose similarly during 3 years of supplementation among 230 men randomly selected to either receive α-tocopherol or not (median values from 1.23 to 1.61 μg/L and from 1.11 to 1.42 μg/L, respectively) or β-carotene or not (median values from 1.32 to 1.72 μg/L and from 1.02 to 1.38 μg/L, respectively).

No difference was found between the 1-year incidences of prostate cancer after visits at which skin yellowing was reported compared with visits without such a report. Supplementation effects did not change in models with skin yellowing as a time-dependent covariate.

No association was observed in the placebo group between the baseline dietary intake or the serum level of vitamin E or β-carotene and the risk of prostate cancer (data not shown).

Discussion

Long-term daily supplementation with 50 mg of α-tocopherol was associated with a substantial reduction in incidence of and mortality from prostate cancer. This intriguing observation suggests that vitamin E has the potential to prevent one of the most common malignant tumors in the North American and European populations. Clinical prostate cancer probably develops in two phases, first into a focal, latent cancer which then changes into invasive, overt cancer *(2,5)*. Large differences have been reported in the incidence of invasive cancer between populations, but not in that of latent cancer, which suggests that external factors are important in the transformation from latent into more aggressive, clinical cancer *(1–3)*. An alternative hypothesis assumes the existence of two types of focal prostate cancer, one truly latent and another malignant from the onset but detected at an early stage *(2,5)*. In this study, a reduction in clinically overt cancers appeared soon after the onset of supplementation, suggesting that α-tocopherol influences the transformation phase of cancer from latent to clinical. α-Tocopherol had no effect on advanced prostate cancer, since the time from diagnosis of clinical prostate cancer to death was not lengthened compared with nonrecipients.

Caution should, however, be exercised when interpreting the findings of this study. Nominally significant chance findings

Table 2. Clinical stages of prostate cancer according to supplementation*

Stage†	Total No. of cases (%)	Supplementation			
		α-Tocopherol, No. (%)	No α-Tocopherol, No. (%)	β-Carotene, No. (%)	No β-Carotene, No. (%)
0	12 (5)	7 (7)	5 (3)	7 (5)	5 (4)
I	42 (17)	19 (19)	23 (16)	18 (13)	24 (22)
II	81 (33)	27 (27)	54 (37)	49 (36)	32 (29)
III	26 (10)	13 (13)	13 (9)	14 (10)	12 (11)
IV	83 (34)	31 (31)	52 (35)	46 (34)	37 (34)
Uncertain	2 (1)	2 (2)	0 (−)	2 (2)	0 (−)
Total	246 (100)	99 (100)	147 (100)	136 (100)	110 (100)

*Includes 123 cases with inadequate clinical information on the status of regional lymph nodes or presence of distant metastases; these cases are classified to be free of lymph node involvement or metastases.

†Staging based on the 4th Edition of the *American Joint Committee on Cancer Manual for Staging of Cancer* (1992).

Table 3. Percent change in the adjusted risk of prostate cancer after long-term supplementation with α-tocopherol or β-carotene, stratified by the median values of baseline characteristics, with *P* values for the interaction between the supplementation effect and the stratified characteristic

Characteristic	Change during α-tocopherol supplementation,* %	*P*	Change during β-carotene supplementation,* %	*P*
Age, y				
<57	−30	.84	63	.21
⩾57	−34		12	
Education				
Less than junior high school	−37	.30	19	.52
Junior high school or more	−11		48	
Vitamin E intake, mg/day				
<10.3	−30	.38	56	.13
⩾10.3	−45		5	
β-Carotene intake, mg/day				
<1.66	−52	.09	72	.04
⩾1.66	−24		0	
Total energy intake, kcal/day				
<2720	−39	.93	54	.12
⩾2720	−37		2	
Total fat intake, g/day				
<117	−33	.53	76	.01
⩾117	−43		−10	
Serum α-tocopherol, mg/L				
<11.5	−35	.77	31	.66
⩾11.5	−30		17	
Serum β-carotene, μg/L				
<171	−35	.75	41	.35
⩾171	−30		11	
Cigarettes/day				
<20	−25	.15	16	.41
⩾20	−51		48	
Years of smoking				
<36	−3	.05	35	.60
⩾36	−43		17	
Body mass index, kg/m^2				
<26	−38	.59	18	.67
⩾26	−29		32	

*In each category, the 95% confidence intervals overlap.

may arise when multiple comparisons are performed, as are done here. An effect due to selection bias is not likely in a large trial that has successful randomization and exhibits similar compliance and dropout rates across the intervention groups. One potential source of bias in end point assessment is an effect of α-tocopherol on prostatic hyperplasia. If supplementation with α-tocopherol retards enlargement of the prostate, relieves clinical symptoms of prostatic hyperplasia, or does both, men receiving it would be less frequently subjected to tests that might also lead to a diagnosis of prostate cancer. α-Tocopherol supplementation was indeed associated with a statistically significant (12%) reduction in visits to a physician for prostatic hyperplasia. Nevertheless, the effect of α-tocopherol on prostate cancer incidence was similar among men who had visited a physician during the study prior to the cancer diagnosis and among those who had not. Second, α-tocopherol had much less, if any, effect on the rate of prostatic hyperplasia diagnosed in the hospital. Third, the increase in serum prostate-specific antigen during supplementation was similar among the men who did or did not receive α-tocopherol, suggesting similar progression of prostatic hyperplasia. Finally, α-tocopherol reduced the incidence of clinical cancers but had no effect on latent cancers, which were more often detected incidental to a urologic examination in which prostatic hyperplasia was recorded.

Bias in the diagnosis of prostate cancer may arise if trial supplementation affected urinary symptoms and subsequent medical contacts. This is not, however, plausible, since patients with prostate cancer who received α-tocopherol were diagnosed while visiting a physician for urinary symptoms as often as patients who did not receive α-tocopherol. Bias may appear due to differences in diagnostic procedures, but no indication of this was found between the supplementation groups. The use of a prostate-specific antigen as a diagnostic tool could not explain the results, because only one case was detected initially by routine screening.

The statistically significant decrease in prostate cancer mortality also suggests a true effect of α-tocopherol. Ascertainment bias is least likely in cases of death due to prostate cancer, since the cases have hardly been missed or overdiagnosed. Also, possible bias due to differences in therapy is unlikely, since surgery and other therapies were equally distributed in the supplementation groups among those who died of prostate cancer.

No association was present in the placebo group between the baseline serum concentration of α-tocopherol, the dietary intake of vitamin E, and the risk of prostate cancer. This finding is in agreement with earlier epidemiological studies focusing on serum or dietary vitamin E and the subsequent risk of prostate cancer *(18–22)*. However, one recent study *(23)* reported that

Table 4. Diagnosis of prostatic hyperplasia in hospital and prostate cancer according to long-term supplementation with α-tocopherol and β-carotene

Diagnosis	Total	Supplementation			
		α-Tocopherol	No α-tocopherol	β-Carotene	No β-carotene
Prostatic hyperplasia without prostatic cancer					
No.	854	418	436	413	441
Rate	5.11	5.00	5.22	4.95	5.27
Prostatic hyperplasia and prostate cancer					
No.	63	33	30	29	34
Rate	0.37	0.39	0.35	0.34	0.40
Latent, %	54				
Prostate cancer without prostatic hyperplasia					
No.	183	66	117	107	76
Rate	1.08	0.78	1.38	1.27	0.90
Latent, %	11				

*Number of cases and rates per 1000 person-years.

low plasma vitamin E levels in smokers were associated with increased mortality from prostate cancer after a 17-year follow-up.

Mechanisms by which α-tocopherol supplementation might prevent the development of clinical prostate cancer can only be speculative *(24,25).* The antioxidant property of vitamin E prevents the propagation of free radical damage in biologic membranes and to critical cellular structures like DNA and proteins. Supplementation for a mean of 4.5 years with selenium, a trace element with indirect antioxidant properties, was associated with a 63% lower incidence of prostate cancer *(26).* Vitamin E may also protect against cancer by enhancing immune functions. Finally, vitamin E has been reported to lower the activity of protein kinase C, a cellular signal transducer that regulates cell proliferation *(25).* In addition, protein kinase C may mediate the contraction of prostate smooth muscle cells that leads to the symptoms of bladder outlet obstruction *(27);* reduced activity of protein kinase C could thus explain the decrease in physician visits due initially to prostatic hyperplasia.

Prostate cancer incidence was 23% higher among men who received β-carotene compared with those who did not. A similar increase occurred in both clinical cancers and in prostate cancer mortality. These effects are unlikely to have been biased by selection or end point assessment. About 34% of the participants who were supplemented with β-carotene reported skin yellowing at least once during the trial compared with 7% of those not receiving β-carotene *(8).* Self-perceived skin yellowing seemed, however, not to be associated with the risk of prostate cancer during the 12 months subsequent to its perception. The observed effect of β-carotene did not change when skin yellowing was controlled taking it into account as a time-dependent covariate. Thus, it is unlikely that the increased incidence of prostate cancer among β-carotene supplemented subjects would be biased due to skin yellowing.

In two other large chemoprevention trials, the Beta-Carotene and Retinol Efficacy Trial *(17)* and the Physicians' Health Study *(28),* supplementation with β-carotene had no effect on prostate cancer incidence. The findings from epidemiologic studies are conflicting, however. Some case-control studies have reported a positive association between vitamin A or β-carotene intake and the risk of prostate cancer, particularly among men aged 70 years or older *(29–33),* while others have found no association or even protection *(34–38).* This inconsistency extends to follow-up study findings *(39–42).* Studies on serum β-carotene level and prostate cancer incidence have shown either an inverse relationship or no association *(20,43).* In the placebo group of this study, baseline dietary intake or serum level of β-carotene and prostate cancer incidence were not statistically related.

There was a trend of increased prostate cancer risk by β-carotene supplementation among alcohol drinkers compared with nondrinkers, but the difference was statistically nonsignificant and there were only 29 cases among 3029 nondrinkers. A similar finding has been reported for lung cancer *(9,17).* There is no obvious mechanism to explain how alcohol and β-carotene together could increase the cancer risk.

In conclusion, the incidence of prostate cancer decreased statistically significantly, by approximately one third, in subjects receiving 50 mg α-tocopherol daily. A similar reduction was observed in prostate cancer mortality. Supplementation with 20 mg β-carotene was associated with a smaller increase in the prostate cancer incidence, but this was not statistically significant. Before vitamin E can be recommended for prostate cancer prevention, further clinical trials are needed.

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Notes

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